PRESCRIBING INFORMATION

[Pr] pms-HYDROXYCHLOROQUINE

(Hydroxychloroquine Sulfate Tablets USP)

200 mg

Anti-Inflammatory - Antimalarial

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(Hydroychloroquine sulfate tablets USP)

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory - Antimalarial

ACTIONS AND CLINICAL PHARMACOLOGY

Hydroxychloroquine has been beneficial for a high percentage of patients with rheumatoid arthritis and lupus erythematosus, especially chronic discoid lupus. The exact mode of action in controlling these diseases is unknown. The action of this compound against malarial parasites is similar to that of chloroquine phosphate.

INDICATIONS AND CLINICAL USE

pms-HYDROXYCHLOROQUINE (hydroxychloroquine sulfate) is indicated for the treatment of rheumatoid arthritis, and discoid and systemic lupus erythematosus, in patients who have not responded satisfactorily to drugs with less potential for serious side effects. It is also Indicated for the suppressive treatment and treatment of acute attacks of malaria due to *P. vivax, P. ma/ariae, P. ova/e,* and susceptible strains of *P. falciparum.* It is not active against the exo-erythrocytlc forms of *P. vivax,* P. *malariae and P. ovale* and therefore will neither prevent infection due to these organisms when given prophylactically, nor prevent relapse of infection due to these organisms. It is highly effective as a suppressive agent in patients with *vivax* or *malariae malaria* in terminating acute attacks and significantly lengthening the interval between treatment and relapse. In patients

with *falciparum malaria,* it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum*.

CONTRAINDICATIONS

Preexisting retinopathy of the *eye,* patients *with known hypersensitivity* to *4-aminoquinoline* compounds and long-term therapy in children.

WARNINGS

Ophthalmic: Irreversibie retinal damage has been observed in some patients who had received long-term or high-dosage 4~aminoquinoline therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Retinopathy is reported to be dose-related and is likely to be increased if recommended dosages are exceeded. When prolonged therapy with any antimalarial compound is contemplated, initial (baseline) and periodic (every three months) ophthalmologic examinations (including visual acuity, expert slit lamp, funduscopic, and visual field tests) should be done.

If there is any indication of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) that are not fully explainable by difficulties of accommodation or coroneal opacities, the drug should be stopped immediately. The patient should be closely observed for possible progression. *Retinal changes (and visual disturbances) may progress even after cessation of therapy* .

Anti-inflammatory: Dermatological reactions to hydroxychloroquine sulfate may occur. It is not recommended for the treatment of psoriasis or porphyria as these conditions may be exacerbated by its use. The preparation should only be used in these conditions, when in the judgment of the physician, the benefit outweighs the risk.

All patients on long term therapy with this preparation should be questioned and examined periodically. Including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

Malaria: Hydroxychloroquine sulfate is not effective against chloroquine-resistant strains *of P. falciparum.* and is not active against the exo-erythrocytic forms of *P. vivax. P. ova/e and P. malarias* and therefore will neither prevent infection due to these organisms when given prophylactically, nor prevent relapse of infection due to these organisms.

Pregnancy: Hydroxychloroquine sulfate should be avoided in pregnancy except for the suppression 'or treatment of malaria when, in the judgment of the physician. the potential benefits outweigh the potential hazards. It should be noted that the 4.aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity,
congenital deafness), retinal hemorrhages and abnormal retinal pigmentation.

Nursing Mothers: Careful consideration should be given to using hydroxychloroquine during lactation, since it has been known to be excreted in small amounts in human breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Pediatric Use: Safety and efficacy has not been established in rheumatoid arthritis or systemic lupus erythematosus in children. Children are especially sensitive to the 4-aminoquinoline compounds. The most reported fatalities follow the accidental ingestion of chloroquine, sometimes in small doses. Patients should be strongly warned to keep these drugs out of the reach of children.

PRECAUTIONS

Observe caution in patients with hepatic or renal disease. in whom a reduction in dosage may be necessary. as well as in those taking medicines known to affect these organs.

Observe caution also in patients with gastrointestinal, neurological, or blood disorders, in those with a sensitivity to quinine, and in glucose-6-phosphate dehydrogenase deficiency, porphyria and psoriasis.

Methods recommended for early diagnosis of retinopathy consist of (1) funduscopic examination of the macula for fine pigmentary disturbances or loss of the foveal reflex and (2) examination of the central visual field with a small red test object for peri central or paracentral scotoma or determination of retinal thresholds to red. Any unexplained visual symptoms, such as light flashes or streaks also should be regarded with suspicion as possible manifestations of retinopathy.

If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) three or four days a week be administered for several months after therapy has been stopped, as acidification of .the urine increases renal excretion of the 4-aminoquinoline compounds by 20 to 90 percent. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

Although the risk of bone-marrow depression is low, periodic blood counts should be obtained in patients requiring prolonged therapy. If any severe blood disorder appears that is not attributable to the disease under treatment, discontinuation of the drug should be considered.

Drug Interaction: Concomitant hydroxychloroquine and digoxin therapy may result in increased serum digoxin levels; serum digoxin levels should be closely monitored in patients receiving combined therapy.

Effects on Ability to Drive and Use Machinery: Patients should be warned about driving and operating machinery since hydroxychloroquine can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced.

ADVERSE REACTIONS

Retinopathy with changes in pigmentation and visual field defects can occur following hydroxychloroquine administration, but is rare. In its early form it appears reversible upon discontinuation of the drug. If allowed to develop however, there may be a risk of progression even after treatment withdrawal.

Corneal changes including edema and opacities have been reported. They are either symptomless or may cause disturbances such as halos, blurring of vision or photophobia. They are reversible upon discontinuation of therapy. Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible may also occur.

Skin rashes sometimes occur; pigmentary changes in skin and mucous membranes, bleaching of hair, and alopecia have also been reported. These usually resolve readily upon cessation of therapy. Isolated cases of exfoliative dermatitis have been reported.

Other adverse reactions include gastrointestinal disturbances such as nausea, diarrhea, anorexia, abdominal pain and, rarely, vomiting. These symptoms usually resolve immediately upon reducing the dose or upon stopping the treatment.

Less frequently, muscle weakness, vertigo, tinnitus, nerve deafness, headache, nervousness, and emotional lability have been reported with this class of drugs.

Rarely, there have been reports of bone marrow depression, cardiomyopathy, neuromyopathy, psychosis and convulsions.

Isolated cases of abnormal liver function tests have been reported and two cases of fulminant hepatic failure have been published

Hydroxychloroquine may exacerbate porphyria and precipitate attacks of psoriasis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with the 4-aminoquinolines is dangerous particulary in infants, as little as 1-2 grams having proved fatal.

Symptoms: The 4-aminoquinoline compounds are very rapidly and completely absorbed following ingestion and in accidental overdosage toxic symptoms may occur within 30 minutes. These consist of headache, drowsiness, visual disturbances, cardiovascular collapse, and convulsions, followed by sudden and early respiratory and cardiac arrest. The ECG may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest,

Treatment: Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital), or gastric lavage until the stomach is completely emptied. If finely powdered activated charcoal is introduced by the stomach tube, after lavage and within 30 minutes after ingestion of the tablets, it may inhibit further intestinal absorption of the drug. To be effective, the dose of activated charcoal should be at least five times the estimated dose of ingested hydroxychloroquine. Convulsions, if present should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultrashort-acting barbiturate may be tried but, if due to anoxia, convulsions should be corrected by oxygen administration, artificial respiration or, in shock with hypotension, by vasopressor therapy. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, has also been advised. Exchange transfusions have been used to reduce the level of 4-aminoquiolines in the blood.

Consideration should be given to administering diazepam parenterally. since studies have reported it beneficial in reversing chloroquine cardiotoxicity.

A patient who survives the acute phase and is asymptomatic should be closely observed fnr at least 6 hours. Fluids may be forced, and sufficient ammonium chloride may be administered for a few days to acidify the urine to help promote urinary excretion.

DOSAGE AND ADMINISTRATION

The dosages cited below are stated in terms of hydroxychloroquine sulfate. One 200 mg tablet is equivalent to 155 mg base. Each dose should be taken with a meal or a glass of milk.

Rheumatoid Arthritis: The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur somewhat early. Several months of therapy may be required before maximum effects can be obtained. If objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months. the drug should be stopped. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial dosage -In adults, from 400 to 600 mg daily. In a few patients, the side effects may require temporary reduction of the initial dosage. Generally. after five to ten days the dose may be gradually increased to the optimum response level, frequently. without return of side effects.

Maintenance dosage - When a good response is obtained (usually in four to twelve weeks), the dosage is reduced by 50 percent and continued at an acceptable maintenance level of 200 to 400 mg daily. The incidence of retinopathy has been reported to be higher when the maintenance dose is exceeded.

If a relapse occurs after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Use in Combination Therapy: pms-HYDROXYCHLOROQUINE (hydroxychloroquine sulfate) may be used safely and effectively in combination with corticosteroids, salicylates, NSAIDS, and methotrexate and other second line therapeutic agents. Corticosteroids and salicylates can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is suggested, it may be done by reducing every four to five days, the dose of cortisone by no more than 5 to 15 mg; of hydrocortisone from 5 to 10 mg; of prednisolone and prednisone from 1 to 2.5 mg; of methylprednisolone and triamcinolone from 1 to 2 mg and dexamethasone from 0.25 to 0.5 mg. Regimens of treatment using other agents than steroids and NSAIDS are under development. No definitive dose combinations have been established.

Lupus Erythematosus: Initially, the average *adult* dose is 400 mg once or twice daily. This may be continued for several weeks or months, depending upon the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200 to 400 mg daily will suffice. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Malaria: Suppression - *In adults,* 400 mg on exactly the same day of each week. *In infants and children,* the weekly suppressive dose is 5 mg base/kg, but should not exceed the adult dose regardless of body weight.

Suppressive therapy should begin two weeks before exposure. When not administered before exposure, give an initial loading dose of 800 mg to adults, or 10 mg base/kg to children in two divided doses, six hours apart. The suppressive therrapy should be continued for eight weeks after leaving the endemic area.

Treatment of the acute attack -*In adults,* an initial loading dose of 800 mg followed by 400 mg in six to eight hours. This is followed by 400 mg on each of the next two days for a total of 2 g of hydroxychloroquine sulfate or 1.55 g base. AIternatively. the administration of a single dose of 800 mg has also proved effective. The dosage for adults may also be calculated by body weight.

For infants and children - dosage calculated by body weight is preferred. A total dose representing 25 mg of base/kg is administered over three days as follows:

First dose:	10 mg base/kg (not to exceed 620 mg base)
Second dose:	5 mg base/kg 6 hours after the first dose (not to exceed 310 mg base)
Third dose:	5 mg base/kg 18 hours after the second dose
Fourth dose:	5 mg base/kg 24 hours after the third dose

For radical cure of *vivax* and *malariae* malaria, concomitant therapy with an 8-aminoquinoline compound is necessary.

AVAILABILITY OF DOSAGE FORMS

pms-HYDROXYCHLOROQUINE (hydroxychloroquine sulfate) is available as: white, film coated, peanut-shaped tablets, containing 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base), with “P” printed in black on one side, bottles of 100.